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LETTER TO THE EDITOR

Renoprotection and blood pressure

To the Editor: The study by Bidani et al elegantly demonstrated that in rats with 5/6 renal ablation blockade of the renin-angiotensin system (RAS) by either an angiotensin-converting enzyme (ACE) inhibitor or by an angiotensin receptor antagonist provides renoprotection, proportionate to the degree of blood pressure (BP) lowering, which was dose dependent [1]. The authors interpret the data to suggest that the renoprotection is only through BP-dependent mechanisms. In fact, the title of the article suggests that there was a lack of evidence of BP-independent protection by RAS blockade after renal ablation in this study. They appear to justify these conclusions because of the tight fit between the level of BP control and the degree of protection as measured by the amount of proteinuria and the percentage of glomerulosclerosis.

In the absence of another group of animals treated with a non-RAS blockading antihypertensive agent to the same levels of blood pressure control as in the animals reported, it is not possible to conclude that there is no role for BP-independent mechanisms associated with RAS blockade in this renal model. Furthermore, it is not even possible, from the data presented, to conclude that the renoprotection is primarily through BP-dependent mechanisms, although that may be the case.

In addition to finding the title misleading, I was surprised that the authors did not even discuss the possibility of BP-independent renoprotection in the ablation model (as studied) except to state that a longer follow-up (they examined these rats after seven weeks) might reveal BP-independent pathways associated with RAS blockade. They also noted that in other models, such as diabetes, RAS may have more significant BP-independent effects.

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REFERENCE

1. Bidani AK, Griffin KA, Bakris G, Picken MM: Lack of evidence of blood pressure-independent protection by renin-angiotensin system blockade after renal ablation. *Kidney Int* 57:1651–1661, 2000.

Reply from the authors

In response to Dr. Porush's criticisms of the conclusions of our study [1], we submit the following facts for his consideration. Several lines of evidence indicate that an exaggerated glomerular transmission of hypertension plays a major role in the pathogenesis of the progressive glomerulosclerosis (GS) observed in the 5/6 ablation model. Moreover, there is an excellent direct correlation between precisely quantitated BP (continuous radiotelemetry) and GS indicating that 60 to 80% of the differences in GS between individual untreated animals can be accounted for by BP differences (r^2 = 0.6 to 0.8) [2–4]. Given such a dominant effect of "BP load" on GS in this model, accurate BP measurements are critical for valid interpretations, the BP-independent protection can only be inferred if the observed protection provided by an agent is disproportionate to the achieved BP reduction. Such was not noted with either benazepril or losartan at any of the dosages.

Dr. Porush considers such evidence insufficient for other antihypertensives. However, a lack of protection comparable to renin-angiotensin system (RAS) blockade may only indicate additional BP-independent deleterious effects of other antihypertensives [3]. In any event, we have previously compared enalapril to both a standard, and a high-dose triple therapy regimen (hydralazine, hydrochlorothiazide and reserpine), using BP radiotelemetry [4]. In contrast to the results obtained using tail-cuff BP measurements, which have provided the primary evidence for BP-independent superiority of RAS blockade, glomeruloprotection in individual animals was found to be proportionate to the achieved BP reductions, regardless of the antihypertensive regimen (r = 0.91 for all 34 rats). However, because of the antihypertensive effectiveness of the single dose of enalapril used, the relationship between BP and GS in enalapril-treated rats could only be examined within a narrow BP range. The present report extends these observations and shows a lack of significant BP-independent nephroprotection by RAS blockade across a wide BP range.

It is possible that BP-independent protective mechanisms may play a more important role in other models or disease states where hypertension is less angiotensin II dependent and/or renal damage is less hypertension mediated. However, we believe our conclusions regarding the lack of evidence of BP-independent protection